AD_____

Award Number: DAMD17-97-1-7087

TITLE: Magnetic Resonance-Guided Interstitial Laser Photocoagulation for the Treatment of Breast Cancer

PRINCIPAL INVESTIGATOR: Steven Harms, M.D.

CONTRACTING ORGANIZATION: University of Arkansas for Medical Sciences
Little Rock, Arkansas 72205-7199

REPORT DATE: September 2000

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2000	Final (1 Aug 97 - 1 Aug 00)

4. TITLE AND SUBTITLE
Magnetic Resonance-Guided Interstitial Laser Photocoagulation for the Treatment of Breast Cancer

5. FUNDING NUMBERS
DAMD17-97-1-7087

6. AUTHOR(S)
Steven Harms, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Arkansas for Medical Sciences
Little Rock, Arkansas 72205-7199

E-MAIL:
steven.Harms@med.va.gov

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

This study explored the use of MRI directed laser ablation as a potential non-surgical treatment method for malignant breast neoplasms.

RODEO MRI was used to determine lesion extent and interactively coordinate therapy. MRI compatible needles were placed with stereotaxic guidance. Biopsy proven malignant breast lesions (30 patients) were treated with a bare tip fiber connected to a diode laser operating at 805 nm for a total of 600-seconds/treatment zone. The effectiveness was established with H & E and PCNA stains.

A total of 68 treatment zones were performed. Surgery (18 mastectomy, 12 lumpectomy) was performed between 2 hours and three days following laser treatment. Serial sectioning of the surgical specimens and stains of the ablation zones correlated in size with the hypointense zones seen on MRI. The average ablation zone size was 10 mm in diameter. Effective cell death was demonstrated in 60/68 zones on PCNA stains. Three patients had minor skin burns that were removed at surgery.

Interactive MRI can be used to coordinate interstitial laser photocoagulation therapy. Laser thermal ablation can effectively destroy malignant breast neoplasms. MRI directed laser therapy offers the potential for treatment of small breast neoplasms without the disfigurement associated with breast conservation surgery.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
37

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

TABLE OF CONTENTS

INTRODUCTION

This research project is investigating the use of MR-directed interstitial laser photocoagulation (ILP) as an innovative alternative to breast conserving surgery. The purpose of this research is to prove that combining minimally-invasive treatment (ILP) with the diagnostic accuracy of MR imaging provides a treatment for breast cancer that is vastly superior cosmetically to breast conserving surgery, and at a significantly lower cost. This research project is designed to (1) demonstrate the potential of ILP for use as a minimally invasive therapy for breast cancer, (2) demonstrate the capability of MR imaging to accurately localize breast cancer and stereotactically position needles for ILP and (3) validate with rigorous MR/pathological correlations the capability of breast MR imaging to accurately determine the treatment zone resulting from ILP.

BACKGROUND

Goals of Breast Cancer Therapy

The goals of current breast cancer treatment include early detection, while the disease is confined to the breast, and local control that results in minimal deformity. Because of the inability to accurately determine the extent of disease before therapy, more extensive treatment is often provided than is actually necessary to cure the disease. This tendency toward over-treatment results in greater morbidity for the patient and high costs for the health care system.

The highly accurate MRI method for breast cancer used by our group was developed with the motivation that better depiction of lesion extent could dramatically improve the treatment of breast cancer. Recent studies demonstrate the capability of ILP for the minimally invasive treatment of solid tumors. In conjunction with Fischer Imaging (Denver, CO), we have developed a prototype stereotaxic biopsy table that is specifically designed for accurate MRI positioning. The goal of this research is to combine high resolution MRI definition of cancer extent, accurate stereotaxic MRI positioning, and ILP into an alternative method for breast conservation surgery. The use of this novel treatment approach would vastly improve cosmesis, reduce morbidity, and lower costs, thus eradicating some of the most detrimental effects of breast cancer therapy.

ILP for Cancer Treatment

ILP has recently been used as a minimally invasive treatment for certain solid tumors. It is based upon the local delivery of low level heat (approximately 50° C) over a period of about 10 minutes. A percutaneous approach is used to place a laser fiber within the lesion using imaging guidance [1-10]. The extent of tissue destruction is a function of fiber position and the temperature gradients created with the interaction of the laser and the cellular components of the tissue. The necrotic tissue that is created by ILP subsequently heals by resorption, regeneration, and/or fibrosis [1-10].

In the United Kingdom, approximately 50 patients with breast cancer have been treated on an experimental protocol using ILP with ultrasound guidance [10]. The analysis of the surgical specimens following this treatment showed obliteration of the lesion, demonstrating the effectiveness of ILP for the treatment of breast carcinoma. However, even though these early results show substantial promise for ILP as a potential treatment alternative for breast cancer, better imaging control than is presently available with sonographic or computed tomographic imaging is needed to determine disease extent and treatment effectiveness [10].

Unlike many solid tumors that have a well-defined interface with adjacent normal tissues, breast cancer infiltrates the surrounding tissue, making the margin difficult to appreciate on most imaging studies and even at surgery. The heterogeneity of breast tissue makes the theoretical prediction of laser heating effectiveness difficult. The surgical correlate of "free margins," obtained with the analysis of the pathology specimen, is needed to determine when ILP has sufficiently destroyed the tumor, leaving a margin of normal tissue. Recent studies have determined that MRI can identify the zones of regional heating resulting from ILP [11-14]. The cellular death induced by ILP produces a phase change that can

be visualized on MR images. This MRI hypointense zone can be used to determine the adequacy of ILP treatment of breast cancer and directly define the extent of cell death. The most important role of MR in this setting is the ability to accurately define tumor and treatment margins.

MR Imaging

A high contrast, high resolution MR imaging method called RODEO (ROtating Delivery of Excitation Off-resonance) was developed by our group specifically for breast cancer imaging. Since the introduction of this new imaging technique in 1991, over 1200 breast examinations have been performed by our research group. This breast MRI experience constitutes one of the world's largest series employing consistent MRI technology and represents the only large series of MRI/serially sectioned pathology correlations. Correlation with rigorous pathological analysis in over 400 serially sectioned mastectomy specimens has validated the accuracy of this method in demonstrating the extent of breast cancer. The sensitivity (94%) and specificity (66%) of RODEO breast MR were twice that of conventional breast imaging when the same cases were evaluated by readers who were blinded to the results of the other examination. In addition, the demonstration by MR imaging of additional, undetected disease foci in 38% of breasts closely approximates the reported prevalence of "subclinical" disease that is reported in rigorous pathological analyses. RODEO imaging can equally detect invasive carcinoma as well as ductal carcinoma *in situ* [24-29]. The remarkable ability of MR imaging to detect tumor margins and extent of disease indicates its potential for successful imaging control during ILP [15-29].

Stereotaxis

Mammographically-directed stereotaxic biopsy has become a recognized alternative to surgical biopsy for certain cases of breast cancer, with stereotaxic biopsy reliability now approaching that of surgical biopsy [30-32]. A variety of prototype stereotaxic devices have been built for MR-directed breast biopsy and needle localization [33-38]. These devices generally consist of components that provide breast immobilization, lesion localization, translation of MR imaging coordinates to spatial coordinates, and needle guidance. Since corrections for gradient nonlinearity are needed for accurate needle localization, all methods use some form of fiducial markers that reference the biopsy system to the MR coordinate system. This enables the accurate positioning of needles in three dimensions for subsequent treatment of the lesion using ILP.

MR Control of ILP Therapy for Breast Cancer

The current surgical approach for breast conservation in the treatment of breast cancer, lumpectomy followed by analysis of the specimen and possible re-excision, requires several days of hospitalization for completion. Pathological analysis is used to determine the adequacy of the surgical resection. Often (40%-70% of cases), the presence of positive margins associated with the lumpectomy specimen requires additional surgery, either re-excision or mastectomy [39-43]. A Japanese study employing rigorous pathological analysis demonstrated a 95% positive margin rate in simulated lumpectomies [44]. In addition, incomplete tumor excisions and residual microscopic carcinoma may be associated with higher recurrence rates, as suggested by the tendency of larger tumors to recur more frequently [43].

MR-guided ILP, on the other hand, could be vastly more efficient and effective, involving only 2 hours of the patient's time for complete obliteration of the tumor. ILP offers a minimally invasive treatment for breast cancer while MRI accurately defines cancer extent and determines the zone of cellular death. In addition, stereotaxic MRI positioning provides the degree of accuracy needed for insertion of the laser and eliminates the need for beast compression. This unique combination of interactive treatment and diagnostic modalities could improve patient care through reduced morbidity, better cosmesis, and removal of the discomfort of breast compression, while, at the same time, lowering health care costs through less surgery and hospitalization time. For the patient with breast cancer, this means that local anesthesia and a needle puncture could replace the current regimen of surgery, hospitalization, general anesthesia, recovery, and breast deformity.

Our study tests the feasibility and outcome of MR-directed ILP in 30 patients with breast cancer who are scheduled for surgical removal of the lesion (mastectomy or lumpectomy).

BODY

EXPERIMENTAL METHODS AND PROCEDURES

We currently have funding to conduct breast MR examinations in a series of patients who have suspicious mammographic or clinical findings. A series of 30 patients who were planning to undergo surgery for removal of the lesion were selected to participate in the trial. Entrance criteria included:

1. Focal lesion on MRI with a maximum lesion diameter of 1.5 cm (may be associated with other lesions, but for the purposes of this pilot study, only one lesion will be treated with MR-guided ILP).
2. No previous radiation therapy to the breast.
3. No previous surgery on the lesion to be treated.
4. No contraindications to MR imaging or gadolinium contrast agent.

Patients were paid $300 for participation in this study.

Stereotaxis

Patient positioning and breast stabilization are essential for obtaining accurate stereotaxis and, thus, successful implementation of MR-guided ILP.

A commercial prototype MR imaging stereotaxic localization and biopsy unit manufactured by Fischer Imaging (Denver, CO) was used initially for this study. This instrument did not work to our satisfaction. Subsequently, an alternative approach was used, based upon a laser guidance system developed in our laboratory.

MR Imaging

All studies employed a high resolution, high contrast RODEO pulse sequence that has the capability of accurate tumor localization based upon validation by over 400 serially sectioned pathology specimens. MR compatible localization wires and biopsy needles are supplied by EZM (Westbury, NY).

After the patient was positioned on the table and the breast had been stabilized with the thermal setting plastic, pre- and post-contrast 128-slice RODEO scans were obtained for localization. Gadopentetate dimeglumine was used as the contrast medium and was administered as an intravenous bolus at 0.1 mmol/kg (8-16 ml). While remaining in position on the stereotaxic table, the patient was moved to the front of the magnet, where the stereotaxic c-arm is located. The patient then received a local anesthetic and, using the c-arm, a needle was placed into the center of the lesion. A laser fiber was then inserted into the needle to the center of the projected treatment zone.

Interstitial Laser Photocoagulation

After the laser fiber had been successfully placed, the patient was returned to the magnet center and laser ablation was begun. The ILP therapy closely followed the methods used by Bown et al. [1-3, 10]. A Nd-YAG laser was used at a power of 1-2 Watts, providing a temperature of about 50° C. The treatment lasted approximately 10 minutes, but total treatment time was determined by the hypointense zone that is seen on MRI.

During laser ablation, MR scans were obtained at 2-minute intervals using rapid 32-slice acquisitions. During heating, a zone of hypointensity appeared on the MR images around the laser tip due to the phase change resulting from the cellular death. When this hypointense zone adequately covered the post-contrast tumor image as well as an adequate disease-free margin, the heating was discontinued.

MR/Pathology Correlations

The gross specimens were sectioned serially. The gross tumor size ranged from 1.0 to 6 cm in the maximum dimension with a mean maximum diameter of 3.0 cm. Histologic examination was performed by routine H & E stains and proliferating cell nuclear antigen stain (PCNA). The determination of size of the treatment zone was achieved with the PCNA stain. The PCNA stain targets actively replicating DNA. Zones of less than 10% PCNA activity compared with surroundings were considered adequately treated. This evaluation was designed to conservatively estimate treatment volume. The procedure works best in zones that are completely within tumor. Zones in normal tissue or on the boundary of normal tissue will not have sufficiently different staining activity from surroundings to accurately depict tissue ablation. The treatment zones were measured in two dimensions and the average measurement used for comparison with the MRI measurement. Final histologies were: infiltrating ductal carcinoma grade I—5 subjects, infiltrating ductal carcinoma grade II—5 subjects, infiltrating ductal carcinoma grade III—16 subjects, and Infiltrating lobular carcinoma—2 subjects. Node dissections or sentinel node procedures were performed on all subjects. The nodal status was as follows: no positive nodes—20 subjects, 1-3 positive nodes—4 subjects, and greater than 3 positive nodes—5 subjects.

Data Analysis

ILP therapy: The capability of ILP as a method for the minimally invasive treatment of breast cancer was measured by rigorous pathological analysis of the surgical specimen. Either the lumpectomy or the mastectomy specimen was serially sectioned with liberal histological sampling. The tissue was analyzed for the location and extent of charring, cellular destruction, and hemorrhage relative to the position of the laser fiber and the margins of the hypointense MRI zone. In particular, we evaluated the consistency of the laser effect and the potential for asymmetric or skipped areas. These data were compared with previous results from animal model studies performed in our laboratory and with results reported in the literature. The data were used to validate the ability of ILP to effectively destroy breast cancer cells *in vivo* and leave a disease-free margin.

MRI localization for stereotaxis: MR images were interpreted prospectively by the PI, and stereotaxic positioning was performed based upon this interpretation. At the end of the study, the ability of radiologists to interpret the MRI information for ILP treatment positioning was evaluated retrospectively. To test the reliability of MRI for lesion identification and localization, three radiologists who were blinded to the initial location selection were asked to select a position for centering the laser. The variability and accuracy of selection of the three radiologists was then determined retrospectively.

MRI treatment control: The MR images that were obtained during ILP were interpreted prospectively by the PI to determine when an adequate hypointense zone was achieved. To test the capability of radiologists to consistently interpret these data, three radiologists were asked to retrospectively define the hypointense zone on the final set of treatment images. The accuracy and variations among radiologists were determined using the pathology gold standard. The histological and biochemical changes in the pathology specimen were analyzed and correlated with the location of the MRI signal changes and the location of the laser fiber tip. The questions we hoped to answer were:

1. Can MRI detect asymmetric heating or potential skip areas?
2. What is the histological appearance of the boundary zone?
3. Is MRI an adequate control method for ILP?

RESULTS AND DISCUSSION

Lesion targeting was performed with pre- and post-contrast high resolution RODEO images. After needle placement, a RODEO image was generated to confirm the accuracy of the stereotaxis. After completion of the laser ablation, a hypointense treatment zone is demonstrated on the post-

contrast RODEO images. The hypointense zone is measured and compared with the PCNA stained size.

A total of 68 treatment zones were performed in 29 patients. A total of 7 zones included some normal tissue and were difficult to correlate with PCNA activity. One of these treatments occurred when the laser tip slipped back into the needle. The other zones that included significant normal tissue were due to inaccuracies in needle placement that occurred early in the development of the stereotaxic localization system. Two zones were incompletely treated and the treatment terminated due to pain. Of the 59 zones where pathologic correlation with PCNA was possible, the average treatment zone diameter on MRI was 1.16 cm (range 0.7 to 2.0 cm). The average diameter of the PCNA activity reduction was 1.01 cm (range 1.75 to 0.55 cm). Considering some distortion that occurs during the preparation of pathologic tissue and the errors in measurement that occur with overlapping zones, the MR appearance could be considered a reasonably accurate representation of treatment zone size.

Three patients with smaller tumors (diameter 2.2, 3.0, and 1.0 cm) had total ablation of the tumor by the laser therapy. Lack of residual contrast enhancement on the MR images indicated complete treatment that was confirmed at pathology. All of the other 26 patients with residual enhancement had residual tumor confirmed at pathology.

All patients tolerated the procedure well. No serious complications developed. The most frequent complaint was due to pressure on the sternum by the MR breast coil. One patient developed a subcutaneous hemorrhage. Most patients sustained less hemorrhage than typically experienced with core needle biopsy. This is attributed to the photocoagulation effects of the laser. The procedure was stopped due to burning pain in two subjects. Only one patient complained of post-procedure burning pain. Of the 12 patients who were surgically treated on subsequent days, minor pain was treated adequately with oral acetomenophen. No narcotics were required. One patient sustained a minor skin burn due to laser treatment of a lesion near the skin. In this case, the lesion was on the medial side of the breast and the skin could not be directly visualized during the treatment. Another patient sustained a minor skin burn when the laser tip slipped back into the needle. Both of these skin burns were removed at surgery. Therefore, the determination of long term cosmetic effects of the skin burns is not possible. The treatment was suspended when the patient experienced pain in the subject where the laser slipped back into the needle. Subsequent to this patient, a luer lock was used to attach the laser to the needle.

This study demonstrates the feasibility of breast MR guided interstitial laser photocoagulation as a minimally invasive alternative to surgical lumpectomy. It is clear that breast MR can effectively determine margins of infiltrating breast cancers (15-29). Current stereotaxic techniques have approached a reliability that would be consistent with most clinical needs (30-38).

Numerous prior studies have determined the ability of ILP to effectively destroy tissue. It is an established treatment alternative for palliation of many tumors (1-9). One would presume that the treatment would also be effective for breast cancer. Yet, the ability to destroy breast cancer by ILP to date is solely based upon histologic evidence (10). When the lumpectomy is performed soon after ILP, the establishment of cell death may be problematic. Routine H & E stains are often inconclusive, especially in regions of normal tissue. We added the PCNA stain to more accurately determine effective ablation. Even these techniques do not directly determine cell death. It is presumed that the markedly diminished DNA replication activity relative to surroundings accurately depicts cell death. Studies performed in the UK with a longer delay between ILP and surgery are more conclusive (10), but ultimately a treatment trial with careful patient follow-up is needed to validate the effectiveness of the treatment method.

A problem with minimally invasive therapy of breast cancer is the need for thorough pathologic evaluation of the specimen. Many breast cancers are a mixture of pathologic components. The most malignant component usually determines the course of adjuvant therapy. A lesion that is thought to be pure DCIS on core biopsy may be found to harbor invasive cancer or microinvasion when the entire lesion is evaluated by pathology. Therefore, a needle diagnosis of DCIS will probably not be eligible for minimally invasive therapy due to the potential for existence of occult invasive disease or microinvasion. Many biochemical markers are now needed for the determination of adjuvant therapy including estrogen receptors, progesterone receptors, her-2-neu, etc. Adequate core samples should be obtained and biochemical markers established prior to minimally invasive therapy.

Despite the potential for greatly improved cosmesis, minimally invasive therapy for breast cancer has not yet been used as a substitute for traditional lumpectomy. There are several reasons for the cautious application of minimally invasive therapy techniques in breast cancer. The use of minimally invasive therapy in most current applications involves palliation of disease, where the therapeutic alternatives incur more risk or not available. For example, metastatic colorectal metastases occur late in the course of disease and the alternative approach, liver resection, incurs significant morbidity. The downside risk of a failed minimally invasive therapy is little. Conversely, early breast cancer has an excellent prognosis if surgically treated. The risk of a failed minimally invasive therapy is a missed opportunity for treatment of a curable disease. These ethical concerns have been a major limitation in the conduction of trials that substitute minimally invasive therapy for traditional lumpectomy. Most validation studies, therefore, follow minimally invasive treatment with surgery with pathologic correlation to determine treatment effectiveness.

Minimally invasive therapy will not be for every patient. As mentioned previously, clear pathologic margins are needed to assure the best prognosis. There is disagreement on what constitutes an adequate margin. It is clear, however, that a 1 cm margin would be acceptable and a reasonable objective for minimally invasive therapy. Therefore, to treat a 1 cm lesion with a 1 cm margin would require a treatment zone of 3 cm. With current bare tip laser fibers, only a 1 cm treatment zone can be reliably produced. To treat a 3 cm zone would require many treatment sessions. The need for many overlapping zones would increase the potential for skip areas and inadequate treatment. New laser systems are being developed for faster treatment over a larger region. Even if larger zones are achieved, the size of the zone may be clinically limited. Lesions near the chest wall are more painful to treat due to sensation in the muscle. Lesions near the skin may result in skin burns and necrosis that would obviate the cosmetic benefits of minimally invasive therapy. The mass of destroyed tissue is slowly absorbed by the body. If the treatment zone is too big, the time to resorption will be increased. Larger volumes of destroyed tissue may not ever be totally absorbed. The presence of a long-standing breast mass after therapy is not a desirable treatment outcome.

Despite the limitations of minimally invasive therapy for breast cancer, the number of potential candidates are increasing. The size of breast cancers at diagnosis is getting smaller due to the widespread use of mammographic screening. Currently about one third of breast cancer is 1 cm or smaller at discovery. Many predict that half of breast cancers will soon be 1 cm or smaller. Many of these, however, will be pure DCIS and will not be amenable to minimally invasive therapy.

The encouraging results from pilot studies and the availability of sufficient clinical tools would indicate that a clinical trial may be warranted in the near future. This trial should evaluate the effectiveness of minimally invasive therapy for the treatment of small breast cancers compared with traditional surgical lumpectomy. It should be noted that the results described in this paper do not test therapeutic effectiveness and that the methods have not been validated for clinical use. The actual use of minimally invasive therapy as a substitute for surgical lumpectomy should only be considered after the completion of a successful, well-controlled clinical trial.

KEY RESEARCH ACCOMPLISHMENTS

- Interstitial laser photocoagulation is an effective method for completely destroying tumor tissue.
- RODEO MRI can accurately demonstrate lesion margins.
- MRI stereotaxis can be used to accurately place needles for ILP.
- RODEO MRI can accurately determine ILP treatment margins.

REPORTABLE OUTCOMES

- **PRESENTATIONS**
  - ***1998***

University of South Florida Medical Center *May 6-8, Key West, FL*
"New Frontiers: MR Imaging of the Breast: Current Status and Future Potential"

University of South Florida College of Medicine Breast Imaging Update *Jul 12-19, 1998, Alaska*
"Breast MRI: The Essentials"

U.S. Public Health Services Office on Women's Health *Sep 8, 1998, Washington, DC*
"International MRI Expert Working Group"; "Current and Potential Role in Local Staging: Implications for Treatment Options"

Colorado Radiological Society, University of Colorado Health Services Center
Oct 8-9, 1998, Denver, CO
"Integration of Breast Magnetic Resonance Imaging with Breast Cancer Treatment"

Southwest Oncology Group *Oct 22-23, 1998, San Antonio, TX*
"Potential Use of Breast MRI in Clinical Trials"

The Wendy & Emery Reves International Breast Cancer Symposium *Oct 16-19, 1998, Dallas, TX*
"RODEO MRI Guided Laser Lumpectomy: The Potential for Treatment Without Disfigurement"

Vanderbilt University Medical Center, Department of Radiology and Radiological Sciences School of Medicine *Nov 2, 1998, Nashville, TN*
"New Frontiers in Breast MRI"

NSABP *Nov 18-19, 1998, Pittsburgh, PA*
"Overview of MRI Current Abilities and Future Needs"

Radiological Society of North America (RSNA) *Nov 29-Dec 4, 1998, Chicago, IL*
"Laser Lumpectomy with Interactive MR Imaging: Histopathological Correlation"

  - **1999**

The International Society for Optical Engineering (SPIE) *Jan 23-24, 1999, San Diego, CA*
"RODEO MRI Guided Laser Ablation of Breast Cancer"

The Sally Jobe Breast Centre – Breast Imaging & Intervention into the 21st Century *Feb 2-12, 1999, Sanibel, FL*
"MRI, An Expanding Role"

16th Annual Miami Breast Cancer Conference *Feb 25-27, 1999, Miami, FL*
"MRI in the Detection, Diagnosis and Staging of Breast Cancer"
"Integration of MRI and Treatment Planning"

Southern Surgeons Club – Annual Meeting *May 3, 1999, Little Rock, AR*
"MRI and Breast"

Arkansas Public Health Association *May 6, 1999, Hot Springs, AR*
"RODEO MRI"

21st Family Practice Intensive Review Course *June 6, 1999, Little Rock, AR*
"MRI & Breast Imaging Update"

Rural Hospital Program Compressed Video Network *June 8, 1999, Little Rock, AR*
"MRI Breast Imaging Techniques"

National Surgical Adjuvant Breast & Bowel Project *June 21, 1999, Toronto, Canada*
"MRI Imaging of the Breast"

Grand Rounds, Yale University *Sept 23-24, 1999, New Haven, CN*
"New Frontiers in Breast MRI";
"Essentials for the Interpretation of Breast MRI"

Educational Symposium, Susan G. Komen Memorial Chapter *Oct 1, 1999, Peoria, ILL*
"Rodeo MRI Directed Laser Lumpectomy: The Potential for Treatment without Deformity"

Breast Cancer Update 1999 *Oct 7-8, 1999, Seattle, WA*
"MRI for Breast Cancer Diagnosis and Staging"

American College of Surgeons Annual Clinical Congress *Oct 10-15, 1999, San Francisco, CA*
"New Techniques in Breast Imaging (Digital, Mammography, MRI, Sestamibi)

93rd Annual Assembly, Southern Medical Association *Nov 10-14, 1999, Dallas, TX*
FIRST PRIZE WINNER:
"RODEO MRI Directed Laser Lumpectomy: An Alternative to Surgery for Benign and Malignant Breast Tumors"

- ***2000***

Breast Imaging and Intervention in the 21st Century: A Multi-Disciplinary Challenge Presented by the Sally Jobe Breast Centre *Feb 14-18, 2000, Fort Meyers, FL*
"Breast MRI--An Expanding Role"

Third Annual Tyler Breast Conference 2000 *Feb 19-20, 2000, Tyler, TX*
"Diagnosis and Imaging of Breasts in the New Millennium"

Radiology: Diagnostic Radiology Review with Emphasis on MRI *Mar 4-5, 2000, Memphis, TN*
University of Tennessee Memphis
"New Frontiers in Breast Imaging"

Society of Surgical Oncology *Mar 16-19, 2000, New Orleans, LA*
Symposium on Minimally Invasive Techniques for Hyperthermic Tumor Ablation
"MR Imaging Integrated with Laser Photocoagulation of Breast Tumors"

Radiological Society of Iowa Annual Meeting *Apr 7-8, 2000, Iowa City, IA*
"Breast MRI: New Frontiers in Clinical Diagnosis and Treatment"

American College of Radiology, Arkansas Chapter *Apr 15, 2000, Little Rock, AR*
"Breast MRI"

American Roentgen Ray Society 100th Annual Meeting *May 7-12, 2000, Washington, DC*
Categorical Course
"Local Breast Staging and Treatment Planning with Breast MRI"

Era of Hope *June 8-11, 2000, Atlanta, GA*
Department of Defense Breast Cancer Research Program Meeting
"RODEO Magnetic Resonance Imaging-Directed Laser Lumpectomy of Breast Cancer"

Annual Meeting, Radiological Society of North America (RSNA) *Nov 26-Dec 1, 2000, Chicago, IL*
"MRI Directed Laser Therapy for Benign and Malignant Breast Neoplasms: Clinical Follow-up and Histologic Conclusions"

- **PUBLICATIONS**

1. Harms SE, Mumtaz H, Hyslop B, Klimberg S, Westbrook K, Hourourian S: Magnetic Resonance Imaging Directed-Laser Lumpectomy. *Breast Diseases, A Year Book Quarterly,* St. Louis; Mosby,1998.

2. Harms SE, Mumtaz H, Hyslop B, Klimberg VS, Westbrook K, Korourian S. RODEO-MRI guided laser ablation of breast cancer. *SPIE* 1999; 3590:484-489.

3. Harms SE, Klimberg VS, Korourian S, Henry-Tillman R, Hyslop WB, Mumtaz H, Mancino AT, Jones MP, Duncan DC, Lindquist D, Cardwell D, Westbrook, K. RODEO Magnetic Resonance Imaging-Directed Laser Lumpectomy of Breast Cancer. *Proceedings Era of Hope* vol 1; 2000, p196.

4. Harms SE MD, Korourian S, Klimberg VS, Henry-Tillman R, Desai A , Price-Jones M, Cardwell D, Lindquist D, Mumtaz M, Westbrook K. MR directed interstitial laser photocoagulation of breast cancer. *Radiology* (to be submitted)

CONCLUSIONS

Preliminary results indicate that:

1. RODEO MRI can accurately identify cancers for laser ablation.
2. Stereotaxic MRI needle positioning can be performed.
3. Fast RODEO MRI can accurately depict zones of ablation for interactive ILP.
4. ILP is an effective method for the minimally-invasive ablation of breast cancer.
5. MRI-guided ILP is safe and is a potential alternative to surgical lumpectomy.
6. MRI-guided ILP may have lower costs and provide better cosmesis than surgical lumpectomy.

PERSONNEL

The following personnel received pay from this research effort:

- Steven E. Harms, M.D.
- Diana M. Lindquist, Ph.D.
- Mary P. Jones, R.N.P.

REFERENCES

1. Bown SG. Phototherapy of tumours. *WorldJSurg* 1983; 7:700-709.
2. Steger AC, Lees WR, Walmsley K, Bown SG. Interstitial laser hyperthermia: a new approach to local destruction of tumors. *Br Med J* 1989; 299:362-365.
3. Masters A, Bown SG. Interstitial laser hyperthermia in tumour therapy. *Ann Chir Gynecol* 1990; 79:244-251.
4. Storm FK, Sliberman AW, Ramming KR, et al. Clinical thermochemotherapy: a controlled trial in advanced cancer patients. *Cancer* 1984; 53:863-868.
5. Matthewson D, Coleridge-Smith P, O'Sullivan JP, Northfield TC, Bown SG. Biological effects of intrahepatic neodymium:yttrium-aluminum-garnet laser photocoagulation in rats. *Gastroenterology* 1987; 93:550-557.
6. Nolsoe CP, Torp-Pedersen S, Burcharth F, Horn T, Pedersen S, Christensen NH, Olldag ES, Andersen PH, Karstrup S, Lorentzen T, Holm HH. Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd-YAG laser with a diffuser tip: a pilot clinical study. *Radiology* 1993; 187:333-337.
7. Amin Z, Donald JJ, Masters A, Kant R, Steger AC, Bown SG, Lees WR. Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. *Radiology* 1993; 187:339-347.
8. Jacques SL, Rastegar S, Motamedi M, et al. Liver photocoagulation with diode laser (805 nm) vs Nd:YAG laser (1064 nm). *Proc SPIE* 1992; 1646:107-117.
9. Schatz SW, Bown SG, Wyman DR, Groves JT, Wilson BC. Low power interstitial Nd-YAG laser photocoagulation in normal rabbit brain. *Lasers in Medical Science* 1992; 7:433-439.
10. Harries SA, Masters A, Lees WR, Scurr J, Cook J, Cooke M, Smith M, Kissin M, Bown SG. *European J of Surgical Oncology* 1993; 19:217-217.65.
11. Jolez FA, Bleier AR, Jakab P Ruenzel PW, Huttl K, Jako GJ. MR imaging of laser-tissue interactions. *Radiology* 1988; 168:249-253.
12. Anzai Y, Lufkin RB, Saxton RE, et al. Nd:YAG interstitial laser phototherapy guided by magnetic resonance imaging in a ex vivo model: dosimetry of laser-MR-tissue interaction. *Laryngoscope* 1991; 101:755-760.
13. Le Bihan D, Delannoy J, Levin RL. Temperature mapping with MR imaging of molecular diffusion: application to hyperthermia. *Radiology* 1989; 171:853-857.
14. Bleier AR, Jolez FA, Cohen MS, et al. Real-time magnetic resonance imaging of laser heat deposition in tissue. *Magn Reson Med* 1991; 21:132-137.
15. Harms SE, Flamig DP, Hesley KL, et al. Breast MRI: rotating delivery of excitation off-resonance: clinical experience with pathologic correlations. *Radiology* 1993;187:493-501.
16. Harms SE, Flamig DP. Staging of breast cancer with magnetic resonance. MRI Clin No Am 1994;2:4.
17. Harms SE, Flamig DP. MR Imaging of the Breast *JMRI* 1993; 3:277-283.
18. Harms SE, Flamig DP. In: Special Course Syllabus Breast Imaging Present and future role of MR imaging. *Radiological Society of North America*, 1994:255-261.
19. Harms SE, Jensen RA, Meiches MD, Flamig DP, Evans WP. Silicone-Suppressed 3D MRI of the Breast using Rotating Delivery of Excitation Off-Resonance. *J Comput Assist Tomogr.* 1995;19:394.
20. Harms SE, Flamig DP, Evans WP, Bown S, Harries SA. MR imaging of the breast: current status and future potential. *AJR.* 1994;163:1039-1047.
21. Harms SE, Flamig DP, Evans WP, Cheek JH, Peters GN, Savino DA, Jones SE. Magnetic resonance imaging of the breast: present and future roles. *Baylor Proceedings* . 1994;7(2):21-26.

22. Cross MJ, Harms SE, Cheek JH, Peters GN, Jones RC. New Horizons in the Diagnosis and Treatment of Breast Cancer Using Magnetic Resonance Imaging. *Am J Surg.* 1993;166:749-755.
23. Pierce WB, Harms SE, Flamig DP, Griffey RH, Evans WP, Hagans JE. Gd-DTPA Enhanced MR imaging of the breast: a new fat suppressed three-dimensional imaging sequence. *Radiology* 1991; 181:757-763.
24. Harms SE, Flamig DP, Hesley KL, Evans WP. Magnetic resonance imaging of the breast. *Magnetic Resonance Quarterly* 1992;8(3):139-155.
25. Harms SE, Flamig DP, Hesley KL, et al. Fat suppressed three-dimensional MR imaging of the breast. *Radioraphics* 1993; 13:247-267.
26. Soderstrom CE, Harms SE, Farrell RS, Pruneda, Flamig DP. Detection with MR imaging of residual tumor in the breast soon after surgery. *AJR* 168:485-8, 1997.
27. Soderstrom CE, Harms SE, Copit DS, Evans WP, Krakos PA, Farrell RS, Flamig DP. 3D RODEO breast MRI of lesions containing ductal carcinoma in situ. *Radiology* 20:427-32, 1996.
28. Miller RW, Harms SE, Alvarez A. Mucinous carcinoma of the breast: potential false negative. *AJR* 167:539-40, 1996.
29. Rodenko GN, Harms SE, Farrell RS, Pruneda JM, Evans WP, Copoit DS, Krakos PA, Flamig DP. MR imaging in the management before surgery of lobular carcinoma of the breast: comparison with pathology. *AJR* 167:1415-9, 1996.
30. Parker SH, Lovin JD, Jobe WE, Burke BJ, Hopper KD, Yakes WF. Nonpalpable breast lesions: stereotactic automated large-core biopsies. *Radiology* 1991; 403-407.
31. Parker SH; Jobe WE; Dennis MA; Stavros AT; Johnson KK, Yakes WF. US-guided automated large-core breast biopsy. *Radiology* 1993; 187:507-511.
32. Jackman RJ, Nowels KW, Shepard MJ, Finkelstein SI, Marzoni FA. Stereotaxic large-core needle biopsy of 450 nonpalpable breast lesions with surgical correlation I lesions with cancer or atypical hyperplasia. *Radiology* 1994; 193:91-95.
33. Heywang-Koebrunner SH, Halle MD, Requardt H, Oellinger HJ, Fischer U, Viehweg P, Speilmann RP. Optimal procedure and coil design for MR imaging-guided transcutaneous needle localization and biopsy. *Radiology* 1994; 193(P):267.
34. Fischer U, Vosshenrich R, Bruhn H, Funke M, Oestmann JW, Grabbe EH. Breast biopsy guided with MR imaging: experience with two stereotaxic systems. Radiology 1994; 193(P):267.
35. Fischer U, Vosshenrich R, Keating D, Bruhn H, Doler W, Oestmann JW, Grabbe E. MR-guided biopsy of suspect breast lesions with a simple stereotaxic add-on-device for surface coils. *Radiology* 1994; 192(1):272-3.
36. Hussman K, Renslo R, Phillips JJ, Fischer HJ, Khalkhali I, Braslau DL, Sinow RM. MR mammographic localization. *Radiology* 1993; 189(3):915-7.
37. Schnall MD, Orel SG, Connick TJ. MR guided biopsy of the breast. *MRI Clin No Am* 1994; 4:585-590.
38. Orel SG, Schnall MD, Newman RW, Powell CM, Torosian MH, Rosato EF. MR imaging-guided localization and biopsy of breast lesions: initial experience. *Radiology* 1994; 193:97-102.
39. Vicini FA, Eberlein TJ, Connolly JL, et al. The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. Ann Surg 1991;214:200-205.
40. Veronesi U, Volterrani F, Luini A, et al. Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J. Cancer* 1990;26:671-673.
41. Ghossein NA, Alpert S, Barba J, et al. Importance of adequate surgical excision prior to radiotherapy in the local control of breast cancer in patients treated conservatively. *Arch Surg* 1992;127:411-415.
42. Kurtz JM, Amalric R, Delouche G, et al. The second ten years: Long term risk of breast conservation in early breast cancer. *Int J Radiat Oncol Biol Phys* 1987;13:1327-1332.
43. Schmidt-Ullrich R, Wazer DE, Tercilla O, et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *Int J Radiation Oncology Biol Phys* 1989; 17:733-738.
44. Haga S; Makita M; Shimizu T; Watanabe O; Imamura H; Kajiwara T; Fujibayashi M. Histopathological study of local residual carcinoma after simulated lumpectomy. *Surg Today* 1995;25:329-33.

DRAFT

MR Directed Interstitial Laser Photocoagulation of Breast Cancer

Steven E. Harms, MD[1], FACR, Sohelia Korourian, MD[2],

V. Suzanne Klimberg MD[3], Ronda Henry-Tillman, MD[3], Ami Desai, MD[1] ,

Mary Price Jones, RN[1], David Cardwell BSE[1], Diana Lindquist, PhD[1],

Hamid Mumtaz, MD, PhD[3], Kent Westbrook, MD[3]

Departments of Radiology[1], Pathology[2], and Surgery[3]

University of Arkansas for Medical Sciences

Little Rock, AR 72205

Address correspondence to:

Steven E. Harms, MD, FACR

Department of Radiology

University of Arkansas for Medical Sciences

4301 W. Markham, Slot 556

Little Rock, AR 72205

(501)257-6622

seharms@earthlink.net

Supported in part by a grant from Department of the Army, US Army

Medical Research and Material Command

Award Number DAMD17-97-1-7087

Key words: Breast neoplasms,MR 00.121411,00.121412, 00.121415,

00.12143

Breast neoplasms, therapeutic radiology, 00.1286, 00.12989

Breast neoplasms, laser therapy

Abstract

PURPOSE: To determine the feasibility of noninvasive magnetic resonance directed interstitial laser photocoagulation (ILP) for the treatment of breast cancer.

MATERIALS AND METHODS: MR compatible needles were placed with stereotaxic guidance after local anesthesia. A total of 59 ILP treatment zones were completed in 29 patients with invasive breast cancer prior to surgery. Interactive monitoring of the laser therapy was performed with dynamic T1 weighted, fat suppressed 3D MR imaging. The treatment zone size was measured on high resolution 3D images and compared to the size of the treatment effects seen with proliferating cell antigen stains (PCNA).

RESULTS: Less than 10% residual PCNA activity was seen in all of the zones that were completed, which indicated a significant therapeutic effect of the laser. The average diameter of the treatment zones measured on MR imaging was 1.16 cm and compared favorably with the pathological average zone diameter of 1.01 cm. Stereotaxic localization was incorrect in the placement of 7 zones. Minor skin burns occurred in 2 patients. The treatment was stopped due to pain in 2 patients.

CONCLUSION: Breast MR imaging can be used to accurately identify breast cancer, stereotaxically place needles for therapy, interactively coordinate the delivery of ILP, and correlate with pathology on the size and effectiveness of the treatment.

Introduction

Modern society favors breast cancer treatment that preserves the cosmetic appearance of the breast. Breast conservation surgery was developed to reduce disfigurement associated with mastectomy with an equivalent therapeutic outcome(1-6). Most patients now prefer lumpectomy over mastectomy surgery. Third party payers widely accept the breast conservation alternative, despite the increased cost and need for radiation therapy.

Small breast cancers ($\leq$ 1 cm) have an excellent prognosis, with a disease-free survival at 20 years approaching 90% (7-12). These results were derived from long-term follow-up on studies where breast conservation was not yet available. It is clear from the outcomes that the disfigurement of mastectomy was not necessary for these small breast cancers.

The excellent prognosis of small cancers indicates a potential for less deforming therapy. The next step beyond surgical lumpectomy is minimally invasive therapy. Minimally invasive therapy has been applied for a variety of solid tumors in other organs including liver, brain, prostate, lung, pancreas, and uterus (13-21). These methods are effective in destroying tissue and the application for the destruction of breast tumors is straightforward (22-27).

A major problem with the application of minimally invasive therapy in breast cancer is the need for knowledge of complete removal of the cancer. It is well-known that subclinical residual disease is present after lumpectomy surgery. A number of rigorous pathologic studies using serial sectioning of mastectomy

specimens have documented the occurrence of otherwise unsuspected foci of disease in about 40% of breasts (28-30). The NSABP (National Adjuvant Breast and Bowel Project) B-06 trial demonstrated a recurrence rate of about 40% in subjects treated with lumpectomy alone compared with a recurrence rate of about 10% in those treated with lumpectomy and radiation (1). The benefit of radiation is attributed to the presence of undetected subclinical disease.

Despite the use of radiation, it is now recognized that the establishment of pathologically-clear surgical margins in the lumpectomy specimen significantly improves the prognosis. Unfortunately, the estimation of tumor extent by conventional imaging and physical examination are inaccurate, resulting in positive pathologic margins in about half of lumpectomy surgeries (31-36). A Japanese study that performed simulated lumpectomy followed by mastectomy and serial section pathology demonstrated positive margins in 90% of cases (37).

The ability of high contrast, high resolution breast MR to accurately depict lesion margins is critical in the use of minimally invasive therapy. A major objective in our serial section correlative study was to demonstrate accuracy of MR margins compared with pathology (38-41). Accurate stereotaxic localization of needles is also a critical technological component of minimally invasive therapy for breast cancer. The capability of stereotaxic MR guidance systems is in evolution. The speed and accuracy of these techniques are improving (42-48).

The purpose of this effort is to demonstrate the feasibility of minimally invasive breast cancer therapy using MR guidance. The study results confirmed

the ability of interstitial laser photocoagulation (ILP) to effectively destroy breast cancer, the ability of MRI to determine treatment zone sizes compared with pathology, and the effectiveness of MRI guidance systems.

Methods

A series of 31 women subjects with biopsy proven carcinoma were entered into the RODEO directed ILP protocol. Informed consent was obtained according to the direction of the University of Arkansas for Medical Sciences Institutional Review Board. One subject was withdrawn from the study due to a MRI malfunction prior to the laser procedure. One subject was withdrawn because the final biopsy report was benign. The 29 subjects completing the protocol ranged in age from 32 to 81 years with a mean of 55.5 years. There were 19 Caucasians, 9 African-American, and 1 native American. Of the treatments, 17 were on the left breast and 12 on the right.

All subjects underwent treatment with surgical resection after the laser procedure. The surgical treatment included lumpectomy in 11 patients and mastectomy in 18 patients. All patients had axillary node evaluations by either sentinel node examination or axillary node dissection. The surgical procedure was usually performed the same day (17 patients). Six patients had surgery the day after the laser procedure. Three patients had the surgery on day four. One patient each had surgery on day 5, day 10, and day 14 after the laser treatment.

The gross specimens were sectioned serially. The gross tumor size ranged from 1.0 to 6 cm in the maximum dimension with a mean maximum

diameter of 3.0 cm. Histologic examination was performed by routine H & E stains and proliferating cell nuclear antigen stain (PCNA). The determination of size of the treatment zone was achieved with the PCNA stain. The PCNA stain targets actively replicating DNA. Zones of less than 10% PCNA activity compared with surroundings were considered adequately treated. The pathologic evaluation was designed to conservatively estimate treatment volume. The PCNA technique is more reliable in zones that are completely within tumor. Zones in normal tissue or on the boundary of normal tissue will not have sufficiently different staining activity from surroundings to accurately depict tissue ablation. The treatment zones were measured in two dimensions and the average measurement used for comparison with the MRI measurement. Final histologies were: infiltrating ductal carcinoma grade I—5 subjects, infiltrating ductal carcinoma grade II—6 subjects, infiltrating ductal carcinoma grade III—16 subjects, and infiltrating lobular carcinoma 2—subjects. Node dissections or sentinel node procedures were performed on all subjects. The nodal status was as follows: no positive nodes—20 subjects, 1-3 positive nodes—4 subjects, and greater than 3 positive nodes—5 subjects.

All MR imaging was performed on a 1.5 Tesla General Electric Signa scanner with 5-8x level software. The RODEO (ROtating Delivery of Excitation Off-resonance) pulse sequence 20/4.6 was employed for all examinations. The image display matrix was 128x256x256 for images before and after treatment. The scan time for a 128 slice scan is about 5 minutes. During treatment, shorter scans of 32 to 64 slices were generated for scan times of about 1 and 2 minutes

respectively . Gadolinium contrast (Nycomed) 0.1 mmol/kg was given before treatment for lesion targeting and after treatment to assess the treatment zone size. The diameter of the hypointense zones were measured in two dimensions on the post-contrast images. The average dimension was compared to the average pathologic dimension.

A prototype stereotaxic needle positioner was used in all cases. This positioner allowed placement of 18 g MR compatible needles (EZM) to within 2 mm of the target. MR images were generated after needle placement to confirm accuracy prior to the laser treatment.

A Diomed-25 continuous wave diode laser operating a 604 nm was used for all procedures. For some patients, a splitter was employed that allowed the use of up to 4 bare tip fibers simultaneously. For most patients, a single bare tip fiber was used but repositioned for each treatment. A standard treatment zone procedure consisted of a pre-char of 18-25 Watts power for 5 seconds followed by a continuous 3 Watts power for 600 seconds.

Local anesthesia was provided with approximately 20 cc of buffered 1% lidocaine and 1% bupivicaine. Oral Xanex 0.5 mg was given for anxiety to most patients. No narcotics were used for pain. If patients complained of burning pain, then more local anesthetic was given or the procedure was terminated. For lesions near the skin on the lateral aspect of the breast, a cold pack was applied locally to reduce the potential for heating the skin.

Results

Lesion targeting was performed with pre- and post-contrast high resolution RODEO images (Fig. 1). After needle placement, a RODEO image was generated to confirm the accuracy of the stereotaxis (Fig.2). After completion of the laser ablation, a hypointense treatment zone is demonstrated on the post-contrast RODEO images (Fig.3). The hypointense zone is measured and compared with the PCNA stained size (Fig.4).

A total of 68 treatment zones were performed in 29 patients. A total of seven zones included some normal tissue and were difficult to correlate with PCNA activity. One of these treatments occurred when the laser tip slipped back into the needle. The other zones that included significant normal tissue were due to inaccuracies in needle placement that occurred early in the development of the stereotaxic localization system. The location of these zones within normal tissue was identified prospectively on the final MR correlative images. Two zones were incompletely treated and the treatment terminated due to pain. Of the 59 zones where pathologic correlation with PCNA was possible, the average treatment zone diameter on MRI was 1.16 cm (range 0.7 to 2.0 cm). The average diameter of the PCNA activity reduction was 1.01 cm (range 1.75 to 0.55 cm). Considering some distortion that occurs during the preparation of pathologic tissue and the errors in measurement that occur with overlapping zones, the MR appearance can be considered a reasonably accurate representation of treatment zone size.

Three patients with smaller tumors (diameter 2.2, 3.0, and 1.0 centimeters) had total ablation of the tumor by the laser therapy. Lack of residual

MR contrast enhancement at the completion of laser therapy indicated effective ablation that was confirmed at pathology. All of the other 26 patients with residual enhancement had residual tumor confirmed at pathology.

All patients tolerated the procedure well. No serious complications developed. The most frequent complaint was due to pressure on the sternum by the MR breast coil. One patient developed a subcutaneous hemorrhage. Most patients sustained less hemorrhage than typically experienced with core needle biopsy. This is attributed to the photocoagulation effects of the laser. The procedure was stopped due to burning pain in two subjects. Only one patient complained of post-procedure burning pain. Of the 12 patients who were surgically treated on subsequent days, minor pain was treated adequately with oral acetaminophen without narcotics. One patient sustained a minor skin burn due to laser treatment of a lesion less than one centimeter from the skin surface. In this case, the lesion was on the medial side of the breast and the skin could not be directly visualized during the treatment. Better guidance and monitoring of medial lesions is needed. Another patient sustained a minor skin burn when the laser tip slipped back into the needle. The treatment was suspended when the patient experienced pain in the subject where the laser slipped back into the needle. Subsequent to this patient, a luer lock was used to stabilize the laser within the trocar introducer. Both of these skin burns were removed at surgery. Therefore, the determination of long term cosmetic effects of the skin burns is not possible.

Discussion

This study demonstrates the feasibility of breast MR guided interstitial laser photocoagulation as a minimally invasive alternative to surgical lumpectomy. It is clear that breast MR can effectively determine margins of infiltrating breast cancers (38-41,49-51). Current stereotaxic techniques have approached a reliability that would be consistent with most clinical needs.(42-48)

Numerous prior studies have determined the ability of ILP to effectively destroy tissue. ILP is an established treatment alternative for palliation of many tumors (13-21). One would presume that the treatment would also be effective for breast cancer. Yet, the ability to destroy breast cancer by ILP to date is solely based upon histologic evidence (22-27). When the lumpectomy is performed soon after ILP, the establishment of cell death may be problematic. Routine H&E stains are often inconclusive, especially in regions of normal tissue. We added the PCNA stain to more accurately determine effective ablation. Even these techniques do not directly determine cell death. It is presumed that the markedly diminished DNA replication activity relative to surroundings accurately depicts cell death. Studies performed in the UK with a longer delay between ILP and surgery are more conclusive (24-26), but ultimately a treatment trial with long-term patient follow-up is needed to validate the effectiveness of the treatment method.

A problem with minimally invasive therapy of breast cancer is the need for thorough pathologic evaluation of the specimen. Many breast cancers are a mixture of pathologic components. The most malignant component usually

determines the course of adjuvant therapy. A lesion that is thought to be pure DCIS on core biopsy may be found to harbor invasive cancer or microinvasion when the entire lesion is evaluated by pathology. Therefore, a needle diagnosis of DCIS will probably not be eligible for minimally invasive therapy due to the potential for existence of occult invasive disease or microinvasion. Many biochemical markers are now needed for the determination of adjuvant therapy including estrogen receptors, progesterone receptors, her-2-neu, etc. Adequate core samples should be obtained and biochemical markers established prior to minimally invasive therapy.

Despite the potential for improved cosmesis, minimally invasive therapy for breast cancer has not yet been used a substitute for traditional lumpectomy. There are several reasons for the cautious application of minimally invasive therapy techniques in breast cancer. The use of minimally invasive therapy in most current applications involves palliation of disease where the therapeutic alternatives incur more risk are not available. For example, metastatic colorectal metastases occur late in the course of disease and the alternative approach, liver resection, incurs significant morbidity. The downside risk of a failed minimally invasive therapy is little. Conversely, early breast cancer has an excellent prognosis if surgically treated. The risk of a failed minimally invasive therapy is a missed opportunity for treatment of a curable disease. These ethical concerns have been a major limitation in the conduct of trials that substitute minimally invasive therapy for traditional lumpectomy. Most validation studies, therefore,

follow minimally invasive treatment with surgery with pathologic correlation to determine treatment effectiveness.

Minimally invasive therapy will not be indicated for every patient. As mentioned previously, clear pathologic margins are needed to assure the best prognosis. There is disagreement on what constitutes an adequate margin. It is clear, however, that a 1 cm margin would be acceptable and a reasonable objective for minimally invasive therapy. Therefore, to treat a 1 cm lesion with a 1 cm margin would require a treatment zone of 3 cm. With current bare tip laser fibers, only a 1 cm treatment zone can be reliably produced. To treat a 3 cm zone would require many treatment sessions. The need for many overlapping zones would increase the potential for skip areas and inadequate treatment. New laser systems are being developed for faster treatment over a larger region. Even if larger zones are achieved, the size of the zone may be clinically limited. Lesions near the chest wall are more painful to treat due to sensation in the muscle. Lesions near the skin (<1cm) may result in skin burns and necrosis that would obviate the cosmetic benefits of minimally invasive therapy. The mass of destroyed tissue is slowly absorbed by the body. If the treatment zone is too big, then the time to resorption will be increased. Larger volumes of destroyed tissue may not ever be totally absorbed. The presence of a longstanding breast mass after therapy is not a desirable treatment outcome.

Despite the limitations of minimally invasive therapy for breast cancer, the number of potential candidates are increasing. The size of breast cancers at diagnosis is getting smaller due to the widespread use of mammographic

screening. Currently about one third of breast cancer is 1 cm or smaller at discovery. Many predict that half of breast cancers will soon be 1 cm or smaller. Many of these, however, will be pure DCIS and will not be amenable to minimally invasive therapy.

The encouraging results from pilot studies and the availability of sufficient clinical tools would indicate that a clinical trial may be warranted in the near future. This trial should evaluate the effectiveness of minimally invasive therapy for the treatment of small breast cancers compared with traditional surgical lumpectomy. It should be noted that the results described in this paper do not test therapeutic effectiveness and that the methods have not been validated for clinical use. The actual use of minimally invasive therapy as a substitute for surgical lumpectomy should only be considered after the completion of a successful, well-controlled clinical trial.

REFERENCES

1. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, Fisher E, Deutsch M, Caplan R, Pilch Y. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. New Engl J Med 1989;320:822-828.
2. Veronesi U, Banfi A, Del Vecchio M, Saccozzi R, Clemente C, Greco M, Luini A, Marubini E, Muscolino G, Rilke F. Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. Eur J Cancer Clin Oncol 1986; 22:1085-1089.
3. Sarrazin D, Le MG, Arriagada R, Arriagada R, Contesso G, Fontaine F, Spielmann M, Rochard F, Le Chevalier T, Lacour J. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol 1989; 14:177-184.
4. Blichert-Toft M. A Danish randomized trial comparing breast conservation with mastectomy in mammary carcinoma. Br J Cancer 1990; 62 (suppl 12):15.
5. Blichert-Toft M, Brincker H, Andersen JA, Andersen KW, Axelsson CK, Mouridsen HT, Dombernowsky P, Overgaard M, Gadeberg C, Knudsen G. A Danish randomized trial comparing breast-preserving therapy with mastectomy in mammary carcinoma: preliminary results. Acta Oncologica 1988;27:671-677.

6. Bader J, Lippman ME, Swain SM. Preliminary report of the NCI early breast cancer (BC) study: a prospective randomized comparison of lumpectomy (L) and radiation (XRT) to mastectomy (M) for Stage I and II BC (abstract). Int J Radiat Oncol Biol Phys 1987;13 (suppl 1):160.
7. Rosen PP, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage 1 (T1N0M0) and stage II (T1 N1M0) breast carcinoma. J Clin Oncol 1989; 7:355-366.
8. Joensuu H, Taikkanen S. Cured of breast cancer. J Clin Oncol 1995;13:62-69.
9. Letton AH, Mason EM, Ramshaw BJ. Twenty-year review of a breast cancer screening project ninety-five percent survival of patients with nonpalpable cancers. Cancer 1996; 77:104-106.
10. Seidman H, Gelb SK, Silvergerg E, Laverda N, Lubera JA: Survival experience in the breast cancer detection demonstration project end results. CA Cancer J Clin 1987; 5: 258-290.
11. Hatschek T, Fagerberg G, Stal O, Sullivan S, Carstensen J, et al. Cytometric characterization and clinical course of breast cancer diagnosed in a population-based screening program. Cancer 1989; 64:1074-1081.
12. Leitner SP, Swern AS, Weinberger D, Duncan LJ, Hetter RVP: Predictors of recurrence for patients with small (one centimeter or less) localized breast cancer (T1a,bN0M0). Cancer 1995; 76:2266-2274.
13. Bown SG. Phototherapy of tumours. World J Surg 1983; 7:700-709.

14. Steger AC, Lees WR, Walmsley K, Bown SG. Interstitial laser hyperthermia: a new approach to local destruction of tumors. Br Med J 1989; 299:362-365.

15. Masters A, Bown SG. Interstitial laser hyperthermia in tumour therapy. Ann Chir Gynaecol 1990; 79:244-251.

16. Storm FK, Sliberman AW, Ramming KR, et al. Clinical thermochemotherapy: a controlled trial in advanced cancer patients. Cancer 1984; 53:863-868.

17. Matthewson D, Coleridge-Smith P, O'Sullivan JP, Northfield TC, Bown SG. Biological effects of intrahepatic neodymium:yttrium-aluminum-garnet laser photocoagulation in rats. Gastroenterology 1987; 93:550-557.

18. Nolsoe CP, Torp-Pedersen S, Burcharth F, Horn T, Pedersen S, Christensen NH, Olldag ES, Andersen PH, Karstrup S, Lorentzen T, Holm HH. Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd-YAG laser with a diffuser tip: a pilot clinical study. Radiology 1993; 187:333-337.

19. Amin Z, Donald JJ, Masters A, Kant R, Steger AC, Bown SG, Lees WR. Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. Radiology 1993; 187:339-347.

20. Jacques SL, Rastegar S, Motamedi M, et al. Liver photocoagulation with diode laser (805 nm) vs Nd:YAG laser (1064 nm). Proceedings SPIE 1992; 1646:107-117.

21. Schatz SW, Bown SG, Wyman DR, Groves JT, Wilson BC. Low power interstitial Nd-YAG laser photocoagulation in normal rabbit brain. Lasers Med Sci 1992; 7:433-439.

22. Harms SE, Mumtaz H, Klimberg SV, Westbrook K. Magnetic resonance imaging-directed laser lumpectomy. *Breast Diseases:* A Year Book Quarterly 1999; 9(4):336-338.

23. Harms SE, Mumtaz H, Hyslop B, Klimberg S, Westbrook K, Kourourian S. RODEO MRI guided laser ablation of breast cancer. Society of Photo-Optical Instrumentation Engineers Proceedings 1999; 3590:484-489.

24. Harries SA, Masters A, Lees WR, Scurr J, Cook J, Cooke M, Smith M, Kissin M, Bown SG. Eur J Surg Oncol 1993; 19:217-217.

25. Harries SA, Amin Z, Smith MEF, et al. Interstitial laser photocoagulation as a treatment for breast cancer. Br J Surg 1994; 81:1617-1619.

26. Mumtaz H, Hall-Craggs MA, Wotherspoon A, Paley M, Bunonaccorsi G, Amin Z, Wilkinson I, Kissin MW, Davidson TI, Taylor I, Bown SG. Laser therapy for breast cancer: MR imaging and histopathologic correlation. Radiology 1996; 200:651.

27. Robinson DS, Parel JM, Denham DB, Gonzalez-Cirre X, Manns F, Milne PJ, Schachner RD, Herron AJ, Comander J, Hauptmann G. Interstitial laser hyperthermia model development for minimally invasive therapy of breast carcinoma. J Am Coll Surg 1998; 186:284-292.

28. Lagios MD, Westdahy PR, Rose MR. The concept and implications of multicentricity in breast carcinoma. in: Sommers SG, Rosen PP (eds). *Pathology Annual.* New York: Appleton-Century-Crofts, 1981, pp 83-102.

29. Holland R, Veling SHJ, Mravunac M, Hendricks JHCL. Histologic multifocality of Tis, T1-2 breast carcinomas: implication for clinical trials of breast-conserving surgery. Cancer 1985; 56:979-90.

30. Schwartz GF, Patchesfsky AS, Feig SA, et al. Multicentricity of nonpalpable breast cancer. Cancer 1980; 45:2913-2916.

31. Ghossein NA, Alpert S, Barba J, et al. Importance of adequate surgical excision prior to radiotherapy in the local control of breast cancer in patients treated conservatively. Arch Surg 1992; 127:411-415.

32. Schmidt-Ullrich R, Wazer DE, Tercilla O, et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. Int J Radiat Oncol Biol Phys 1989; 17:733-738.

33. Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB, Eberlein TJ, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. Cancer 1994; 74:1746-1751.

34. Spivak B, Khanna MM, Tafra L, Juillard G, Giulano AE. Margin status and local recurrence after breast-conserving surgery. Arch Surg 1994; 129:952-957.

35. Pezner RD, Lipsett JA, Desai K, Vora N, Terz J, Hill LR, Luk KH. To boost or not to boost: decreasing radiation therapy in conservative breast cancer treatment when "inked" tumor resection margins are pathologically free of cancer. Int J Radiat Oncol, Biol, Phys 1988; 14:873-877.

36. Ryoo MC, Kagan AR, Wollin M, Tome MA, Tedeschi MA, Rao AR, Hintz BL, et al: Prognostic factors for recurrence in the conservative management of early breast cancer: A 25 year follow-up. Int J Radit Oncol, Biol, Phys 1989; 17:719-725.

37. Haga S; Makita M; Shimizu T; Watanabe O; Imamura H; Kajiwara T; Fujibayashi M. Histopathological study of local residual carcinoma after simulated lumpectomy. Surg Today 1995; 25:329-33.

38. Harms SE, Flamig DP, Hesley KL, et al. Breast MRI: rotating delivery of excitation off-resonance: clinical experience with pathologic correlations. Radiology 1993; 187:493-501.

39. Soderstrom CE, Harms SE, Copit DS, Evans WP, Krakos PA, Farrell RS, Flamig DP. 3D RODEO breast MRI of lesions containing ductal carcinoma in situ. Radiology 1996; 201:427-432.

40. Rodenko GN, Harms SE, Farrell RS, Pruneda JM, Evans WP, Copit DS, Krakos PA, Flamig DP. MR imaging in the management before surgery of lobular carcinoma of the breast: correlation with pathology. *AJR.* 1996; 167:1415

41. Abraham DC, Jones RC, Jones SE, Cheek JH, Peters GN, Knox SM, Grant MD, Hampe DW, Savino DA, Harms SE. Evaluation of Neoadjuvant

chemotherapeutic response in locally advanced breast cancer by magnetic resonance imaging. Cancer 1996;78(1):91-100.

42. deSouza NM, Gilderdale DJ, Coutts GA, et al. Magnetic resonance imaging guided breast biopsy using a frameless stereotactic technique. Clin Radiol 1996; 51:425.

43. Heywang-Koebrunner SH, Halle MD, Requardt H, Oellinger HJ, Fischer U, Viehweg P, Speilmann RP. Optimal procedure and coil design for MR imaging-guided transcutaneous needle localization and biopsy. Radiology 1994; 193(P):267.

44. Fischer U, Vosshenrich R, Keating D, Bruhn H, Doler W, Oestmann JW, Grabbe E. MR-guided biopsy of suspect breast lesions with a simple stereotaxic add-on-device for surface coils. Radiology 1994; 192(1) 272-273.

45. Hussman K, Renslo R, Phillips JJ, Fischer HJ, Khalkhali I, Braslau DL, Sinow RM. MR Mammographic Localization. Radiology 1993; 189(3):915-917.

46. Schnall MD, Orel SG, Connick TJ. MR guided biopsy of the breast. MRI Clin No Am 1994; 4:585-590.

47. Orel SG, Schnall MD, Newman RW, Powell CM, Torosian MH, Rosato EF. MR imaging-guided localization and biopsy of breast lesions: initial experience. Radiology 1994; 193:97-102.

48. Cardwell DM, Harms SE, Lindquist D, Jones MP, Duncan DC, Hronas TN. Laser directed portable MRI stereotactic system. Radiology 2000; 217P:268.

49. Orel SG, Schnall MD, LiVolsi VA, Troupin RH. Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. Radiology 1994; 190:485-493.

50. Daniel BL, Yen Y-F, Glover GH, Ikeda DM, Birdwell RL, Sawyer-Glover AM, Black JW, Plevritis SK, Jeffrey SS, Herfkens RJ. Breast disease: dynamic spiral MR imaging. Radiology 1998; 209:499.

51. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, Schild HH. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 1999; 211:101-110.

Acknowledgement: We thank Jan McKee for her editorial assistance, Helen Beam for assuring communication and coordination, and the technologists of UAMS for their assistance in the performance of this clinical trial.